

II

“ THE PROGNOSIS AND TREATMENT OF NEURO-SYPHILIS ”

DISCUSSION

THE PRESIDENT, after expressing appreciation of Dr Riddoch's wide survey of the subject, raised the question of the etiological importance of syphilis in progressive muscular atrophy on which Dr. Wilson in the *Guy's Hospital Reports*, and more recently Christophe (Thèse de Paris, 1927) had written. It would also be interesting to hear Dr. Riddoch's view on spirochætal infection as the cause of disseminated sclerosis, on which Dr. Douglas Adams, of Glasgow, had done much work. There was also the question why, if there was a special strain of the syphilitic spirochæte with a selective affinity for the central nervous system, the skin so often escaped when the nervous system, also of ectodermal origin, was invaded. In connection with Dr. Riddoch's remarks on the occasional untoward effects of the powerful arseno-benzol preparations, he recalled an old observation of Erb's to the effect that cases of syphilis vigorously treated by mercury might be thought to be attacked very early by tabes, because mercurial neuritis (pseudo-tabes) resulted. Recently Surgeon-Commander W. I. G. (Brit. Med. Journ., 1924, ii., 224) had shown by Hi. van den Bergh's test for bilirubin the frequent hepatic insufficiency in syphilitic patients treated with arseno-benzol, the latent jaundice thus revealed being a danger signal. Malarial treatment of general paralysis of the insane probably acted in virtue of shock therapy. Colonel L. W. Harrison would remember a series of cases of men with syphilis but without nervous complications who, in the course of intravenous injections of arseno-benzol preparations appeared to have been accidentally infected with malaria, and that several of them succumbed.

COLONEL L. W. HARRISON said he had appreciated very much Dr. Riddoch's thoughtful and critical address, from which he had learned a great deal. Dr. Riddoch

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had, indeed, covered the ground so well that there seemed little to question him on.

He had been interested in what the opener said about silver salvarsan. Dr. Riddoch seemed disinclined to use it, apparently because tabetic pains were aggravated during the course. Later, Dr. Riddoch spoke of the better results from malarial treatment, but mentioned that during the malarial paroxysms the patients' symptoms were aggravated. It therefore did not seem right to condemn silver salvarsan because the patients seemed to be rather worse while the treatment was being carried out. Probably the aggravation was a manifestation of a Hexheimer's reaction, an indication that the remedy was "touching the spot." His own impression was that silver salvarsan left the patient better, that it achieved more than did a course of intravenous injection of any other arsenobenzol preparation. He was now, however, inclined even more than formerly to give arsenobenzol compounds deep subcutaneously, using one of the "sulpho" compounds. His impression had been that one got better results in neuro-syphilis, including tabes, from the subcutaneous injection of an arsenobenzol preparation than from its intravenous use, and this impression was confirmed by Stokes. He asked if Dr. Riddoch considered there was anything in the idea that when it was given subcutaneously some of the remedy was absorbed along the peri-neural lymph channels.

It was of interest to hear that the malarial treatment seemed to cause no change in the cerebro-spinal fluid picture, as one was constantly reading articles which advocated that in syphilis at much earlier stages, with a persistently positive Wassermann reaction in the cerebro-spinal fluid, the malarial treatment should be instituted ~~it once~~, for example in cases in which two years or so ~~after~~ infection many courses of treatment had produced no change in the reactions. Some people said that the cerebro-spinal fluid picture did change, but they recommended that examination of the cerebro-spinal fluid ~~should~~ not be undertaken under less than three months after the malarial paroxysms ceased.

He asked for Dr. Riddoch's views as to the treatment of neuro-syphilis with intensive iodine, *i.e.*, huge doses of one of the iodine preparations. At the present day he thought there was a tendency to give too little iodine.

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In some cases which he had recently treated with heavy doses of iodide of potassium by the mouth, or by using sodium iodide intravenously, results seemed much better than when it was given in smaller doses. His impression was that bismuth was much more valuable in the treatment of neuro-syphilis than was mercury, particularly when used in combination with big doses of potassium iodide.

He was also interested in Dr. Riddoch's finding that 50 per cent. of cases of tabes, when first seen, gave negative findings in the blood. That was not the experience at his own clinic, but perhaps at the latter the cases attended at a later stage.

Dr. C. P. SYMONDS said he had listened with great interest to the opening paper, and, in the main, he agreed with all Dr. Riddoch said. The great difficulty in assessing the value of any treatment of neuro-syphilis was the comparatively small experience of the evolution of the untreated disease. Therefore it was of great value to collect experiences of cases of syphilis which did not come under treatment until a comparatively late stage. From his experience of such cases he would say that, with the exception of syphilitic encephalitis, neuro-syphilis was a self-limited disease, and that made it difficult to know what part was played by treatment in a given case. At neurological clinics he believed there was now seen a smaller proportion of late ataxic cases than formerly, no doubt because of the use of the modern anti-syphilitic remedies.

He agreed that arsenical preparations were most valuable, and that was true of the parenchymatous forms of neuro-syphilis. He commenced as an unbeliever in arsenic, and for some time he tried treating one case of tabes with mercury, the next with arsenic, and so on. After that had been carried on for three years it was found that, on the whole, the cases given mercury were doing so much worse than those on N.A.B., that all cases were subsequently treated with the latter. In early days the doses used were too small; they should be pushed to the patient's toleration limit. Even if in this energetic treatment one now and again had a case of jaundice or of exfoliative dermatitis, the price was a fair one to pay for the good results obtained in other respects. In some forms of neuro-syphilis, especially the meningeal form, iodide was probably the most valuable, and he ag

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with Colonel Harrison as to the inadequacy of the usual doses. One drachm of potassium iodide should be given thrice daily in meningeal syphilis.

And he agreed with Dr. Riddoch that the guide for treatment should be furnished by the patient's general condition and the evolution of the disease in him, rather than by the serological reactions. From the first it should be realised that no great improvement in the symptoms could be expected, for there was sure to have occurred a good deal of permanent damage in the central nervous system. It was, therefore, well to give the patient, at the first interview, a rough outline of what the disease might lead to if untreated and point out to him that he must not be disappointed if some of the symptoms could not be relieved. In the neuro-syphilitic, having given an intensive course, he reviewed the clinical situation, and if there had been no progress in the physical signs and no further development, he got the patient to come in six months for a prophylactic course of weekly injections of N.A.B., and full doses of mercury and iodide of potassium for a month, but telling him to come at once if he developed acute symptoms. He was told that if he remained healthy he should attend once a year for the rest of his life for prophylactic treatment.

With regard to the treatment of G.P.I. by malaria, his experience had been derived mainly from statistics. The value of the malarial treatment would depend on the patient's condition at the time and upon the nature of his occupation. In the case of the G.P.I. patient, life was prolonged by a number of years in a proportion of cases, though whether under these circumstances life was worth living was another matter. But "G.P.I." was but a pigeon-hole artificially constructed. Though syphilitic encephalitis usually progressed to what was called G.P.I., and ended fatally, yet occasionally it was spontaneously arrested, though the number of cases in which this took place was much smaller than in tabes.

Prognosis in neuro-syphilis was very difficult when of the parenchymatous form, especially in tabes, in which disease he did not think it was ever safe to prognose anything. Some of the cases of tabes went rapidly to the bad, whatever treatment was adopted, but others seemed to be arrested spontaneously—(without treatment because they had not been recognised).

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The form of neuro-syphilis in which the prognosis was better than in any other was syphilitic endarteritis in a young person, leading to cerebral thrombosis and hemiplegia. Though these cases could not be expected to improve beyond a certain point, they seemed unlikely to develop any further evidence of neuro-syphilis.

Another group which carried a good prognosis if adequately treated was cerebral meningitis of syphilitic nature, with headache and cranial palsy.

He was ignorant of the paper the President referred to, but there were some cases of amyotrophic lateral sclerosis which one could not always distinguish, by clinical means, from the non-specific cases in which there was a positive reaction in the blood and cerebro-spinal fluid, or, more often, in the latter, and in a proportion of them, anti-syphilitic treatment might arrest the course of the disease. It was well in every case of progressive muscular atrophy to have the Wassermann done in both fluids, as well as inquiring as to a history of venereal infection. Following that practice had yielded him some good results.

Dr. H. M. HANSCHALL said that in the twelve cases of G.P.I. he had treated by malaria he had not noted a change in the cerebro-spinal fluid, but in two of the cases of tabes which he had treated by malaria the C.S.F. Wassermann had become negative three months after the malaria was over. He did not know whether that was a matter of chance, or was due to the malaria, or would prove a permanent change.

Mr. WANSEY BAYLY read the following :—

A lady who had been married for twelve years was sent to me by Dr. Jane Hawthorne in October, 1923.

The patient stated that except that she had always been delicate, and had been subject to "nervous breakdowns" for the last eight years, she was well until December, 1921, when she noticed areas of hyperæsthesia of skin on both legs, for which she consulted a doctor in July, 1922, who gave her nine intravenous injections of 0.3 grm. N.A.B. and inunctions of mercury. She stated that her Wassermann was reported to be positive. This treatment she considered did harm rather than good as she stated that shooting pains developed in the arms and legs, and transient itchings of the skin, and that the ground felt soft under her feet, and that she occasionally had bladder pains and incontinence. She stated that she

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had recently found out that her doctor had treated her for syphilis, at which she was very indignant. There was no history obtainable of primary, secondary or tertiary syphilis, except that she stated that she had some patchy loss of hair soon after marriage.

She appeared to be hysterical, worried and ill, and complained of great exhaustion after slight exertion. Her knee, ankle and elbow jerks were absent, her pupils were equal and extremely sluggish to light, her gait was weak and slightly staggering, but not ataxic or spastic, and she had slight Rombergism. Her W.R. of blood was negative.

I considered that she was a tabetic, but in order to protect myself from her possible future anger, I had a consultation with the late Sir Frederick Mott, who confirmed the diagnosis of tabes, and in view of her neurotic condition, advised that no lumbar puncture should be made, and that syphilis should not be mentioned. He considered that 75 per cent. of her symptoms were functional. He agreed to the course of protein shock and bismuth therapy that I had suggested.

After two months' treatment of subcutaneous injections of Phlogetan as recommended by Professor Fischer of Prague, and intramuscular injections of Levaditi's Neo-Trepol, she was much improved, and I sent her to the country for two months. On her return she stated that the ground no longer felt soft, and that she could walk for two miles without undue fatigue, and that the transient itching of the skin was very much better. She had had no further pains in the bladder and no incontinence.

I gave her a second course of Phlogetan and bismuth, and towards the end of the course shooting pains returned, and though no incontinence returned, she stated that when passing water "pain tingled down to the toes," and that she had some pains round the waist. I then gave her four months' rest from treatment, and on her return in October, 1924, I found her much improved. She stated that she had had no shooting pains in limbs and waist, and no bladder pains for two months, and that she could walk for three to four hours without fatigue. The stagger in gait had disappeared, but the reflexes were unchanged.

In December, 1924, she returned for another course, after the second injection of Phlogetan she felt sick

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and ill, and the pains returned, so she decided to stop treatment.

I did not see her again, but in 1925 she asked me to send a *résumé* of her case to a hospital for nervous diseases, which she proposed attending for financial reasons. This I did. I believe that she there received ordinary anti-syphilitic treatment, and rapidly grew worse. I heard no more of her until July or August, 1926, when I heard from Dr. Jane Hawthorne, who had visited her in Horton Mental Hospital as a friend, that she was demented, unable to feed herself, emaciated, and had incontinence of urine and fæces, and that death was expected shortly.

Imagine my astonishment when early this month as I was walking along Marylebone Road, this lady, whom I imagined had been dead for some months, came up and addressed me, looking well, speaking quite sensibly, and walking with a firm and healthy gait. She informed me that malarial treatment had cured her. I expressed astonishment at her miraculous recovery, and she gave me the address of the mental hospital and the name of her doctor (Dr. W. D. Nicol), who is here to-night, so that I might obtain details of her case for the information of this Society.

Dr. Nicol very kindly sent me a *résumé* of her case while in the Horton Mental Hospital. She was admitted in June, 1926, mentally confused and unable to give any account of herself, not even her age or address. It was stated that immediately prior to admission she had developed grandiose ideas and had ordered two grand pianos, and had run up extravagant bills. Her gait was ataxic, and there was marked Rombergism, both knee jerks were absent, the pupils differed in size, and though the right was inactive to light, the left reacted sluggishly. The Wassermann of the C.S.F. was positive, as was the cell count, protein content and colloidal gold test.

Her condition rapidly grew worse, so that she became bedridden, wet and dirty, picked herself, developed tremor of tongue and fingers, and had to be hand-fed. She was given open-air treatment and slightly improved, and in November, 1926, it was decided to give her malarial treatment, and she was inoculated by a mosquito infected with benign tertian. She was allowed to have fourteen peaks of fever, ten of which ranged between 104° and 105° F. She was extremely ill during the fe

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but from the time the malaria was terminated by quinine, her mental and physical condition slowly improved.

In February, 1927, she was sent out of hospital on trial, and was discharged recovered in April, when her mentality and memory were good, with no signs of deterioration. There was no Rombergism, and the left pupil reacted briskly to light, though the right was sluggish. As this is the most remarkable case I personally have met of the, at least temporary, complete recovery of a very advanced case of neuro-syphilis, I have ventured to give you the full six years' history of the case from apparent onset to apparent recovery.

Dr. NICOL said he was glad to give the Society some of the results of treatment of G.P.I. at the Horton Mental Hospital, Epsom. A little more than two years ago an arrangement was arrived at between the Board of Control and the Ministry of Health and the London County Council, to treat cases of G.P.I. with malaria. The mental hospital of which Colonel Lord was Superintendent was selected, with Colonel James from the Ministry as Tropical Medicine adviser. The original strain was obtained from a sailor, a native of Madagascar. During the last year thirty batches of mosquitoes had been used, and over 300 patients from sixty-nine hospitals had been infected with benign tertian malaria. The cases he would be mentioning were all women, and were all certified insane. The diagnosis of G.P.I. in each case had been verified by serological tests. The admissions were not all recent cases, many had had mental symptoms for a year or two before admission. When the patient spoken of by Mr. Bayly came to Epsom, she was so ill that it was regarded as out of the question to give her malarial treatment, but as her physical condition showed some improvement later, it was decided to take the risk. There was a risk, because from the literature cases showed a mortality of 6 per cent., and the risk occurred especially when terminating the malaria by giving quinine. Fifteen out of fifty cases so treated at Epsom had been discharged as cured, and seventeen of the fifty were now in hospital a good deal improved. He thought five of them would be discharged next month. Ten had not got any better mentally, though all cases had improved physically, and their lives had been made more tolerable, as they were able to look after themselves, and were no longer helpless



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and dirty. Many of them were employed in the hospital. Of the fifty, six had died, but in no case did the death have any connection with the malaria. Improvement in nearly all the cases was accompanied by a loss of the tremors of lips and fingers, and the articulation improved. Lumbar puncture was performed one month, three months, and six months afterwards, and in some cases the Wassermann after the malaria was less strongly positive than before it. This gave no indication, however, of the future course of the case. None of the patients showed the true parietic curve after treatment. The experience at Horton was that the patients who did worst were paranoid subjects. He had not noticed that patients got much worse while the treatment was in progress. Even patients who had been in a state of mania went through the course fairly well.

The mosquito was used to convey the disease, blood infection was not employed. The attack of malaria could be divided into three stages: (1) the initial attack, when the temperature fluctuated, and was slightly intermittent, but was not true quotidian or tertian; (2) the typical fever; (3) the terminal stage. Patients were not allowed to run a temperature above 105° F.; at that point cold-sponging was carried out. Eight to ten peaks of temperature were allowed. When the rigor started, the temperature was taken every fifteen minutes, in that way a temperature was noted which might be missed with four-hourly takings. It is important to estimate the severity of the attack by examining the blood daily. Using a one-twelfth oil-immersion lens, if on an average of twenty-five fields there were thirty to thirty-five parasites per field, that was a definite indication to terminate the attack. In 85 per cent. of cases the primary attack of malaria in benign tertian was quotidian, not tertian, and some patients with a daily rise of temperature got very ill. By giving one dose of 5-gr. quinine, patients stopped fever from ten to fifteen days, during which time they were enabled to regain some strength, and after that the fever would recommence and was less severe. Other indications for terminating the attack were severe vomiting and collapse, cyanosis, paralytic seizures, restlessness, albuminuria, jaundice. Only two cases of jaundice occurred in the series. During the fever plenty of fluid to drink was given. Daily enemata were found necessary

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owing to severe constipation. Attacks of malaria were terminated by giving quinine gr. v. t.d.s. for ten days. It was found that malarial relapses occurred in 50 per cent. of cases, and a relapse might occur as long as ten months after the primary attack. During the convalescence iron and other tonics were given, and then salvarsan was used.

No doubt the whole success in this treatment was based on the early diagnosis of G.P.I.

Dr. WOODHOUSE asked whether in some of the cases treated by malaria there was any difference in the leucocytes in the cerebro-spinal fluid. That was so in cases treated with fairly large doses of sodium iodide. Perhaps N.A.B. rendered the spirochæte in a position to be attacked better. In cases of tabes, at St. Thomas's a systematic examination of the cerebro-spinal fluid was attempted in out-patients, but there was no large proportion of reactions.

Dr. C. H. SEMON asked whether Dr. Riddoch or the members knew anything about Saprovitin, which, it was said, could take the place of malaria in treatment of general paralysis and similar conditions. It consisted of a living bacterial emulsion, and could be given to out-patients without ill effects. At the Royal Northern Hospital a case had been tried on it. He had already been treated by malaria, induced by Colonel James, but his condition had relapsed somewhat a year later. The patient had now had three of the five courses of Saprovitin, and he had improved.

With regard to the difficulty in using silver salvarsan owing to the colour, at the hospital they used a three-piece syringe, with a glass channel at the end of it, into which distilled water could be sucked up. On vein puncture the blood could be seen to come back into the water, thus ensuring that the vein had been properly entered.

Dr. GREENFIELD said the malaria therapy was started empirically; only later was the pathology of treated cases studied in a series of cases in which patients had died after malarial treatment. In some of the cases immediately after the malarial treatment there was a much more severe inflammatory reaction in the brain than was ever found in ordinary general paralysis, as though a more acute fight was being put up. After the malarial

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treatment the spirochæte disappeared quickly from the brain. After this acute stage following malaria there occurred a stage more resembling the tertiary syphilitic stage. This was a stage at which the brain was recovering, but showed tertiary lesions differing from those of general paralysis. That suggested that by means of shock therapy there occurred a change in the reaction of the patient to the disease, and it also explained why there was an improvement in the cerebro-spinal fluid in the later cases in which it could not be cleared by ordinary treatment.

Dr. SHARPE said that one case admitted to hospital, a child, had a strongly positive blood and cerebro-spinal fluid, and the usual changes. She had two courses of malarial treatment, followed by bismuth. The blood was now absolutely Wassermann negative, and the cerebro-spinal fluid normal. She was practically insane. She was a "spoilt" child, but it was a very interesting result.